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EDWARD DAVISON AND JAMES I. WELLS	Art Unit: 121
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FOR: "IMPROVEMENTS IN PHARMACEUTICALLY ACCEPTABLE SALTS"	
OUR REF.: SPC 7025 (PLC 423)	

DECLARATION UNDER RULE 132

I, JAMES I. WELLS declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

1. I was awarded the degree of Bachelor of Science with Honours in Pharmacy from Brighton Polytechnic, the degree of Master of Science with Distinction in Pharmaceutical Technology from the University of London and the degree of Doctor of Philosophy from Liverpool Polytechnic. I am a member of the Royal Pharmaceutical Society of Great Britain and the Institute of Packaging, and a Qualified Person in the Pharmaceutical Industry (as specified in S.I. 1977/1053 and Directive 75/319/EEC). I am also author of the textbook entitled "Pharmaceutical Preformulation: The physicochemical characteristics of drug substances" (James I. Wells, published by Ellis Horwood, Chichester, England, 1988). Since 1981, I have been employed by Pfizer Limited, Sandwich, England in Pharmaceutical Research and Development, and, since 1983, as a group leader responsible for all aspects of pharmaceutical product development.

2. Although amlodipine is effective as the free base, in practice it is best administered in the form of a pharmaceutically acceptable acid addition salt. Whereas certain previously-known salts of amlodipine have satisfied some of the necessary criteria for pharmaceutical formulation, none have satisfied them all, and even the previously preferred maleate (EP-A-89167/US 4,572,909), whilst exhibiting excellent solubility, has unacceptable stability characteristics. Hence the formulation studies were carried out under my direction to compare a range of pharmaceutically acceptable acid addition salts of amlodipine using four physicochemical criteria: namely solubility and saturated solution pH; solid state stability; hygroscopicity; and "processability", as described below:-

(a) Solubility and saturated solution pH

Generally it is known in the art that a good aqueous solubility is necessary for good bioavailability. Usually a solubility of greater than 1 mg ml^{-1} at a pH from 1 to 7.5 is sought, although higher solubilities are required to formulate injections. In addition, salts which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility.

The aqueous solubility was measure by the separate equilibration (by continuous agitation) of an excess of each salt form in distilled water overnight at 37°C, then by assay, after centrifugation and suitable dilution with 0.01 N methanolic HCl, using u.v. spectroscopy.

The saturated solution pH was measured after centrifugation, but prior to dilution using 0.01N methanolic HCl, by conventional means.

As can be seen from Table 1, the besylate salt of amlodipine exhibits favourable solubility and saturated solution pH characteristics.

TABLE 1

Salt	Solubility mg ml^{-1}	pH at saturation
Benzenesulphonate (besylate)	4.6	6.6
Toluenesulphonate (tosylate)	0.9	5.9
Methanesulphonate (mesylate)	>25	3.1
Succinate	4.4	4.9
Salicylate	1.0	7.0
Maleate	4.5	4.8
Acetate	>50	6.6
Hydrochloride	>50	3.5
Free base	0.09	-

(b) Solid state stability

Good stability in the solid state is very important for tablets and capsules.

In order to screen for solid state stability, each of the salts was blended with a powder vehicle and formed into tablets or capsules containing 5% by weight of the appropriate salt form. In the case of tablets, the powder vehicle was microcrystalline cellulose and anhydrous dibasic calcium phosphate (50:50), and the mixture was compressed into tablets under 1 ton pressure. In the case of capsules, the powder vehicle was mannitol and dried maize starch (80:20). These were then stored in sealed vials at 50 and 75°C for up to three weeks. The drug and any break-down products were extracted with methanol:chloroform (50:50) and separated on silica tlc plates using a variety of solvent systems.

The results were compared and the salts ranked according to the number and amount of break-down products produced (Table 2). The besylate emerged as the most stable and the hydrochloride the least stable salt form.

TABLE 2

Salt	Stability	
Besylate	+++	↑
Mesylate	++	
Tosylate	++	INCREASING STABILITY
Succinate	+	
Salicylate	-	
Maleate	-	
Acetate	—	
Hydrochloride	---	

(c) Hygroscopicity

In order to provide stable solid formulations it is desirable to have a non-hygroscopic salt. In the solid state where drug content is high, absorbed films of moisture can act as a vector for hydrolysis and chemical break-down. It is the hygroscopic nature of a drug or it's salt which contributes to the free moisture which is normally responsible for instability.

Separate samples of the besylate, tosylate, mesylate, succinate, salicylate, maleate, acetate and hydrochloride salts of amlodipine were each stored over both saturated NaCl at 37°C and saturated $BaCl_2.2H_2O$ at 30°C, to give 75 and 90% relative humidities respectively. Changes in sample weight were recorded for up to seven days and related to their molecular weights to quantify the extent of hydrate formation, if any.

Of the salt forms tested, only the maleate, tosylate and besylate salts do not pick up any moisture when exposed to 75% relative humidity at 37°C for 24 hours. Even when exposed to 90% relative humidity at 30°C for 3 days, both the

besylate and maleate remain anhydrous whilst the tosylate formed the dihydrate salt. Therefore the besylate salt can be considered to be non-hygroscopic and thus provides stable formulations, minimising the risk of intrinsic chemical breakdown.

(d) "Processability"

Good "processability" characteristics of an acceptable salt are very important and are principally defined by the compression properties and also the ability not to stick or adhere to the tablet-making machinery.

For high dose formulations, good compressability is very important to make elegant tablets. With lower dose tablets, the need for good compressability can be eliminated to a certain extent by the use of suitable diluting excipients called compression aids. Microcrystalline cellulose is a commonly used compression aid. However, whatever the dose, the adhesion of the drug to the punches of the tablet machine must be avoided. When drug accumulates on the punch surfaces this causes the tablet surface to become pitted and therefore unacceptable. Also, adhering of the drug in this way results in high ejection forces when removing the tablet from the machine. In practice it is possible to reduce adhering by wet-massing, careful selection of excipients and the use of high levels of anti-adherents, e.g. magnesium stearate (which also functions as a boundary lubricant). However selection of a salt with a limited adhesion propensity minimises these problems.

In order to compare the adhesion propensity of the various salts of amlodipine, the following procedure was carried out using conventional tablet-making machinery. Fifty tablets containing a mixture of calcium sulphate dihydrate (this excipient was used instead of anhydrous calcium phosphate in this study because it was less abrasive, which results in higher levels of drug adhesion, and experimentally allowed easier discrimination between the various salt forms),

microcrystalline cellulose and the appropriate salt of amlodipine (47.5:47.5:5) were made, the material adhering to the tablet punch was then extracted using methanol and the amount measured spectrometrically. This procedure was then repeated for runs of 100, 150, 200, 250 and 300 tablets. After each run the amount of material adhering to the tablet punch was measured after extraction with methanol. The values are plotted and an average value calculated from the slope of the line produced. The amount of each salt of amlodipine measured as adhering to the tablet punch, and relative to the maleate salt, is shown in Table 3.

TABLE 3

Salt	Stickiness	
	μg Amlodipine salt cm^{-2} $tablet^{-1}$	Relative to maleate (%)
Mesylate	1.16	58
Besylate	1.17	59
Tosylate	1.95	98
Maleate	1.98	100
Free base	2.02	102
Succinate	2.39	121
Hydrochloride	2.51	127
Salicylate	2.85	144
Acetate	-	-

Clearly the besylate is much less adherent than the maleate. Whilst the mesylate also shows good "processability", it tends to be isolated as the anhydride, but this equilibrates to the monohydrate leading to variable composition after manufacture which also makes it unacceptable for use in tablets.

3. The results given above are the true results obtained.

4. In summary, the besylate salt of amlodipine has been found to possess a highly desirable combination of physicochemical properties, such properties being unpredictable both individually and collectively. Thus this salt form is outstandingly suitable for the preparation of pharmaceutical formulations of amlodipine that are of major commercial importance.

3rd October 1988

J. I. WELLS

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